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Kurt J Smith[1], Ryan L Hoiland[2], Ryan Grove[1], Hamish McKirdy[1], Louise Naylor [1], Philip N Ainslie[2], Daniel J Green[1,3]

[1]Cardiovascular Research Group, School of Human Sciences (Exercise and Sport Science),

The University of Western Australia, Perth, Australia;

[2]Centre for Hearth Lung and Vascular Health, School of Health and Exercise Sciences, University of British Columbia,

[3]Research Institute for Sport and Exercise Sciences, John Moores Liverpool University, UK

Corresponding Author:
Kurt J. Smith
Kurt.smith@uwa.edu.au
610431698502
School of Human Sciences M408
35 Stirling Highway, Nedlands, 6000
The University of Western Australia

Abstract

Introduction: Maintenance of adequate cerebral perfusion is essential to brain function and health, but the role of arterial shear stress in the regulation of cerebrovascular responses has not been definitively addressed. We hypothesized that, if shear stress is a key regulator of arterial dilation, then matched increases in shear induced by distinct physiological stimuli (hypercapnia vs exercise), would induce similar changes in dilation of the internal carotid [ICA] and vertebral [VA] arteries.

Methods: Healthy male (n=10) participants attended the laboratory 3 times, during which they were asked to breathe a mild hypercapnic gas mixture (CO2:~4.5%CO_2), or perform a submaximal cycling test (EX; 60%HRreserve), or rest quietly (CTRL). Blood flow, diameter and shear rate were assessed in the ICA (BL;10, 20, 30mins, post) and VA (BL;15, 25mins, post) using duplex ultrasound. Middle cerebral artery blood flow velocity (MCAv) was maintained at 30% above baseline values by adjusting CO_2 and exercise intensity.

Results: During CO2 and EX, blood flow and shear rate through the ICA and VA were significantly elevated ($p<0.001$) compared to CTRL, but no differences existed between CO2 and EX. The change in ICA and VA diameter from baseline in response to CO2 (5.3±0.8 and 4.4±2.0%) and EX (4.7±0.7 and 4.7±2.2%) were similar, but both were significantly elevated compared to CTRL condition (0.10±0.10 and -0.58±0.13 %,all $p<0.001$).

Conclusion: This is the first study in humans to compare the vasodilator impact of distinct stimuli that increase cerebral artery shear stress in humans. Our findings indicate that matched levels of shear, irrespective of their driving stimulus, induce similar changes in extra-cranial arterial diameter. This study therefore suggests an important mechanistic role for the endothelium in regulating cerebral artery dilation in response to common physiological stimuli in vivo. Interventions that enhance endothelial function may mitigate age-related decline in cerebrovascular vasodilator function in humans.

Introduction

In conduit arteries such as the coronary,[1] brachial,[2] radial,[3] and femoral,[4,5] it is well established that intra-arterial shear stress regulates endothelium-dependent vasoreactivity and that episodic increases in shear can induce anti-atherogenic adaptation in paracrine transduction pathways, including the nitric oxide (NO)-dilator system. Shear-mediated stimulation of the endothelium is a key mechanism responsible for vasodilation through these conduit arteries in humans.[6]

Exercise increases blood flow to the brain in humans.[7] Traditionally, the explanation for this has been attributed to a combination of physiological stimuli, including changes in arterial blood gases, blood pressure and metabolism.[8] Another possible mechanism involves changes in arterial shear stress and consequent endothelium-mediated dilation.[9] Recently, we demonstrated vasodilation of extra-cranial feed arteries as a result of hypercapnia induced increases in brain blood flow and shear stress in vivo.[10,11] However, the impact of shear stress on cerebrovascular responses during exercise has not previously been investigated.

In the current study, we propose that shear stress is involved in regulating cerebrovascular function during exercise in humans. We therefore examined the impact of matched elevations in arterial shear stress, induced by distinct mechanisms (exercise vs hypercapnia), with the hypothesis that similar internal carotid artery diameter responses would be observed.

Methods

Participants

Ten healthy male participants (age, 25±6 years; weight, 74.14±7.03kg; height, 2.11±0.21m) were recruited for the study. All participants were non-smokers, with a BMI<30, free of

cardiovascular, respiratory, cerebrovascular, musculoskeletal and/or metabolic diseases. The study was approved by the University of Western Australia's Human Research Ethics Committee. The participants were informed of all experimental procedures and associated risk. Participants provided written informed consent before the commencement of the study.

Experimental design

After inclusion, participants were tested at the Cardiovascular Research Laboratory on three occasions separated by >48hours at the same time of day. Each visit consisted of one of three randomly assigned interventional protocols (Control [CTRL], Hypercapnia [CO_2], or Exercise [EX]). Subjects arrived after fasting for a minimum of 6 hrs, with 24 hr abstinence from alcohol, caffeine and vigorous exercise. Upon arrival, participants were instrumented and underwent a 10 min rest period in a semi-recumbent position. Baseline (BL) recordings of the primary outcome measures were then collected during a further 5-minute period of quiet rest. Following baseline measures, subjects participated in one of three interventions: 1) 30-minutes of hypercapnia (see below); 2) 30-minutes of exercise at 60% heart rate (HR) reserve; or 3) 30-minutes of rest (control day). Cerebrovascular (transcranial Doppler and duplex vascular ultrasound) and cardiorespiratory assessments were collected throughout each condition.

Experimental procedures

Cerebrovascular assessments

Non-invasive insonation via 2MHz transcranial Doppler ultrasound (TCD; Spencer Technologies, Seattle, WA) was used to assess blood flow velocity in the middle (MCAv) and posterior (PCAv) cerebral arteries. The cerebral arteries were identified and optimised according to their signal depth, waveform and velocities, according to previously published

guidelines.12 The MCAv and PCAv were continuously recorded at baseline, throughout the 30-minutes of each intervention, and during post-intervention assessments.

Blood velocity and diameter of the internal carotid artery (ICA) and vertebral (VA) arteries (VA) were measured using a 10-15MHz multi-frequency linear array vascular ultrasound (Terason T3200, Teratech, Burlington, MA).[13] Whilst ICA recordings were captured at 10, 20 and 30 minutes of the intervention, the VA recording were captured at 15 and 25 minutes of the intervention. Baseline and post-intervention recordings (5–10 minutes post) were collected for both the ICA and VA. All of the ICA and VA recordings were screen captured and stored as video files for offline analysis.[14]

Cardiorespiratory measurements

All cardiorespiratory variables were sampled continuously throughout the protocol at 1000Hz via an analogue-to-digital converter (Powerlab, 16/30; ADInstruments, Colorado Springs, CO). Partial pressure of oxygen and carbon dioxide were assessed using a gas analyser (ADInstruments, Colorado Springs, CO), heart rate (HR) was measured by a 3-lead electrocardiogram (ECG; ADI bioamp ML132), and beat-to-beat blood pressure by finger photoplethysmography (Finometer PRO, Finapres Medical Systems, Amsterdam, Netherlands).

Experimental interventions

Hypercapnia (CO_2) condition

Hypercapnia was used as a stimulus to elevate cerebral blood flow (CBF) and shear stress for 30 minutes. Hypercapnia was achieved via breathing an air mixture (4.5% CO_2, 21% O_2, and balance N_2) through a spirometer connected to a Douglas bag. The participants were seated in

a semi-recumbent position whilst hypercapnia was induced. Simultaneous assessment of intracranial velocity (measured by transcranial Doppler of the left MCA and right PCA) and beat-by-beat extracranial blood flow (measurement by Duplex ultrasonography of the ICA and VA) was assessed along with beat-to-beat arterial pressure (Finometer Pro, Amsterdam, Netherlands). Continuous monitoring of MCAv was used as an index of real-time change in cerebrovascular shear stress. If necessary, the concentration of inspired CO_2 was altered (range 3-6%) to achieve the desired increase in arterial shear stress (~30% above baseline).

Exercise condition

Participants cycled at submaximal intensity (~60% heart rate (HR) reserve = 100-120bpm) for 30-minutes to maintain a steady increase in CBF measures throughout the exercise condition. As with the hypercapnia intervention, continuous intracranial blood velocity and extra-cranial blood flow were measured at the same time points during the intervention. The MCAv during the 30-minute intervention was closely monitored to ensure that an elevated CBF and shear stress was achieved (~30% above baseline, to match the CO_2 condition).

Control condition

Participants sat in a semi-recumbent position for 30-minutes. Continuous intracranial blood velocity and extra-cranial blood flow were measured at the same time points as the interventions above.

Statistics

Statistical and graphing analysis was performed using GraphPad PRISM 6.01 software (GraphPad Software, LaJolla, CA, USA). All parameters were compared within-subjects using 2-way ANOVA repeated-measures. Bonferroni-correction for multiple comparisons were used

for all post-hoc analysis. Finally, a correlation was performed between the absolute change in arterial shear stress and diameter in the ICA and VA. Statistical significance was assumed at $p<0.05$. All data are reported as mean ± SD unless otherwise specified.

Results

All cardiorespiratory and cerebrovascular values, for the anterior (ICA, MCA) and posterior (VA, PCA) cerebral arteries, are provided in tables 1 and 2.

Cardiorespiratory measures

No changes were observed for any of the cardiorespiratory measures assessed during the 30 minute CTRL condition (Table 1 and 2).

During the CO2 and EX, MAP increased ($p<0.01$), but returned toward baseline values post-intervention (Tables 1 and 2). The magnitude of increase in MAP was similar between the CO_2 and EX conditions, except for the post-intervention timepoint ($p<0.001$). No change in MAP was observed throughout the CTRL condition, but both CO_2 and EX MAP data were significantly elevated throughout the intervention period, relative to the CTRL trial ($p<0.001$).

The CO_2 and CTRL conditions did not elicit any changes in HR, whereas the EX condition was associated with elevated HR compared to baseline values and by comparison to the other conditions during the intervention period. $P_{ET}O_2$ and $P_{ET}CO_2$ were elevated throughout the CO_2 intervention ($p<0.001$), compared to baseline values and also when compared to the CTRL condition. EX had a small impact on $P_{ET}CO_2$ compared to baseline values.

Cerebrovascular measures

No changes in either MCAv or PCAv were observed during CTRL. When all time points were considered, similar mean increases, from BL, were observed in response to CO2 (28.1±3.4 and 23.3±2.8%) and EX (27.7±3.8 and 19.6 ± .3.0%) in the in MCAv and PCAv, respectively ($p<0.001$). All MCAv and PCAv values were greater during the EX and CO2 conditions relative to the CTRL data (Figure 1; $p<0.001$).

In terms of duplex ultrasound data collected in both the ICA and VA, the EX and CO2 conditions stimulated similar magnitudes of increase in blood flow, blood velocity and shear rate ($p < 0.001$), relative to baseline value. Furthermore, blood flow, velocity and SR data collected under the CO2 and EX conditions were elevated compared to the CTRL condition throughout the intervention period (Figure 1; $p<0.001$).

No changes ICA or VA diameter were observed during CTRL. In contrast, ICA and VA diameters increased from baseline values during both CO2 and EX (Table 1; $p<0.001$). The increases in diameter, in both arteries, were higher than the changes observed in the CTRL condition at all timepoints, except for the VA diameters 10 minutes post intervention. However, there were no differences in the changes in diameter observed when the CO2 and EX conditions were compared.

Discussion

Our findings indicate that matched increases in cerebrovascular shear stress, irrespective of the eliciting stimulus (CO2 or EX), induce similar increases in extra-cranial artery diameter in humans. This study therefore provides novel evidence that arterial shear stress, alongside

changes in blood gases and pressure, is an important stimulus regulating extracranial cerebral conduit artery dilation in vivo. Given that repetitive episodic increases in shear stress beneficially impact arterial function and structure,[6] our novel observation provides a mechanistic basis for linking exercise, physical activity and cerebrovascular health in humans.

It is well established that endothelium-dependent mechanisms play a key role in shear stress mediated vasodilation of coronary and peripheral arteries in humans.[1,3-5,15] These studies have established a role for paracrine hormones such as NO and prostacyclin in vasomotor regulation, for example, in response to exercise. However, few studies have addressed the impact of changes in arterial shear on human cerebral vasodilator function in vivo. In animals, classic studies have established that increases in flow and shear stress through isolated cerebral conduit arteries trigger endothelial-mediated vasodilation.[16] Recently, Raignault et al.[17] illustrated that the cerebrovascular endothelium optimally couples shear stress to eNOS-mediated dilation under physiological pulse pressures, in contrast to static flow conditions. This strongly infers that changes in cerebral arteries are responsive to a pulsatile environment and that shear stress sensitivity and consequent production of NO are optimised under in vivo conditions.[17] It is also well established that carotid artery remodelling as a result of chronic changes in flow is dependent upon the presence of a functional endothelial layer,[18] implicating shear- and NO-mediated mechanisms in arterial structural adaptation. Collectively these findings, in animals, support a key role for shear-mediated endothelial-dependent dilation of extra- and intra-cranial cerebral conduit arteries. However, few studies have addressed the role of shear in regulating the cerebral vasculature in humans.

Recently we characterised the timecourse and response of ICA dilation to changes in shear using duplex ultrasound with high temporal resolution edge-detection and wall-tracking in

healthy subjects.[10] We concluded that, in response to a sustained hypercapnic stimulus (5-mins), dilation of the ICA occurs subsequent to marked increases in intra-arterial blood flow and shear stress. In a subsequent experiment,[11] a brief hypercapnic stimulus (30 secs) triggered similar ICA vasodilator response patterns to the sustained 5 min stimulus, despite the absence of simultaneous increases in end tidal CO_2, implicating shear, rather than hyercapnia driven dilation. The current study advances these findings by illustrating that exercise, a shear eliciting stimulus which induces smaller changes in arterial blood gas concentrations, nonetheless increases extra-cranial artery dilation in humans. Our findings indicate that elevating shear during exercise, to a level that matches that associated with hypercapnia, elicits similar dilation of both the ICA and VA.

This study is one of the few to have assessed extra-cranial artery responses to exercise in humans. Whilst some previous studies have assessed blood flow responses in the ICA during exercise,[7,19,20] these have not specifically focused on changes in arterial diameter or shear stress. Furthermore, no study, to date, has reported changes in ICA diameter or shear during a prolonged bout of exercise. We observed significant ICA dilation during exercise in all subjects. Our findings therefore raise the possibility that exercise-mediated and shear-driven increases in the bioavailability of endothelium-derived dilators such as NO may counteract other vasoactive pathways, such as the increase in sympathetic drive associated with some forms of exercise. Indeed, functional sympatholysis is a well-established phenomenon in skeletal muscle arterioles during exercise.[21,22] Ultimately, vasomotor drive to vascular smooth muscle, in response to a stimulus as complex and integrative as exercise, will reflect the balance between dilator and constrictor mechanisms and our study supports a role in this regard for shear-mediation vasodilation.

This is the first study that has assessed VA diameter and shear relationships during EX, CO2 and CTRL conditions in humans. Our findings indicate that the vertebral arteries exhibit dilator responses which are similar to those observed in the ICA. Only two previous studies, to our knowledge, have recorded VA blood flows during exercise in humans, but these did not address changes observed in either diameter or shear.[7,20] When considered in concert with our contemporaneous MCA and PCA observations, our ICA and VA data therefore indicate that cerebral shear and artery dilation occur in both the anterior and posterior cerebral circulation in response to both EX and CO2 in humans.

An interesting minor finding of the present study relates to change in shear and artery diameter following the cessation of exercise. We continued data collection in the post-exercise period, at different time-points in the ICA (5 mins post) and VA (10 mins post). Dilation remained somewhat elevated 5 mins post-exercise, whereas it had returned to near resting baseline levels 10-min post-exertion. These findings provide some insight into the timecourse of change in extra-cranial artery diameter following a relatively prolonged exercise stimulus.

There are several limitations of the current experiment. We recruited and studied young male subjects. The impact of cyclical changes in sex hormones on shear-mediated cerebrovascular function and health would be an important follow up study in women. Although our findings suggest that exercise and hypercapnia elicited shear-mediated endothelial dependent dilation of the ICA and VA, we did not utilize a NO antagonist to address specific endothelial pathways. Future studies, particularly in animals, involving more invasive approaches, for example endothelial denudation and/or pharmacological blockade, would advance our understanding of the endothelial dependency of extra-cranial dilation. We think it unlikely that direct effects of the EX and CO2 conditions on extra-cranial diameter were the result of increases in blood

pressure, per se. Increases in intra-arterial pressure, and associated transmural pressure, are typically associated with myogenic mediated vasoconstriction,[23] whereas we observed dilation in all subjects under both conditions. $P_{ET}CO_2$ was somewhat elevated above baseline in EX condition and we are therefore unable to exclude the possibility that CO_2 directly induces extra-cranial dilation during exercise. Nonetheless, we are unaware of any experimental evidence indicating that this occurs in conduit arteries and, furthermore, we recently demonstrated that ICA dilation in the presence of elevated shear occurs in the absence of changes in $P_{ET}CO_2$. Finally, we acknowledge that the limitations of TCD impair our ability to extrapolate our extracranial diameter responses to changes in shear stress, to intracranial changes that may have simultaneously occurred in the MCA and PCA. However, the intention of our study was to focus on the ICA and VA responses, with intracranial measures collected primarily in order to confirm that matching of shear in each intervention was successful.

Conclusion

We have demonstrated, for the first time in humans, that matched increases in shear stress through the extra-cranial cerebral conduit arteries in response to distinct stimuli induce similar levels of vasodilation. Our novel findings quantified vasodilator changes in both the anterior and posterior extra-cranial conduit arteries, suggesting an important mechanistic role for the endothelium in regulating cerebrovascular function in humans. Interventions that enhance endothelial function may mitigate age-related decline in cerebrovascular vasodilator function in humans.

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Figures

Table 1. Anterior cerebral blood flow and cardiorespiratory measurements during control (CTRL), carbon dioxide (CO2), and exercise (EX) interventions (n=10).

Measure	Condition	Time (min) BL		10		20		30		Post		INT
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
MAP (mmHg)	CTRL	88	11	90	8	90	8	93	8	91	9	
	CO2	87	7.6	100*φ	10	104*φ	14	102*φ	14	96	11	**
	EX	82φ	11	102*φ	10	102*φ	9.5	100*φ	7.7	86*ψ	15.8	
HR (bpm)	CTRL	64	7	64	9	67	7	67	7	63	7	
	CO2	66	8	70	9	74	9	70	7	63	7	**
	EX φψ	70	8	115φψ	11	115φψ	7	118φψ	7	80φψ	11	
PetO2 (mmHg)	CTRL	95.2	6.8	97.7	3.2	98.5	5	100.4	6.9	96	6.2	
	CO2 φ	97.4	5	128*φ	2.9	130*φ	1.9	130 *φ	2.3	96	7.8	**
	EX ψ	95.2	6.5	96.6ψ	7.8	95.8ψ	7.6	96.0ψ	7.8	96.8	4.1	
PetCO2 (mmHg)	CTRL	42.7	4	42.4	2.7	41.9	3.6	41.3	3.6	41.6	3.4	
	CO2 φ	42.3	3	46.9*φ	2.4	46.3*φ	2.3	46.2*φ	2.2	41.3	2.5	**
	EX	41.6	3.1	44.7*	4.9	44.7*	4.5	44.4φ	5.2	40.8	2.4	
Q_{ICA} (ml.min^{-1})	CTRL	297	24.8	289	20.8	278	21.4	278	24.4	264	24.1	
	CO2	262	18.8	368*φ	23.8	380*φ	30.5	354*φ	25.1	256	16.1	**
	EX	274	16.9	361*φ	19.7	368*φ	29.6	394*φ	26	282	24.1	
ICA Diam (mm)	CTL	5.2	0.2	5.2	0.2	5.2	0.2	5.2	0.2	5.2	0.2	
	CO2	5.0 φ	0.1	5.3*	0.1	5.3*	0.1	5.4* φ	0.1	5.2	0.1	**
	EX	5.1	0.2	5.2	0.2	5.4*	0.2	5.4* φ	0.2	5.3	0.2	
ICA Vel (cm.s^{-1})	CTRL	41.1	1.5	40.8	1.2	39.7	1.7	39.6	1.6	38.3	2.2	
	CO2	39	2.1	49.5*φ	2.8	49.7*φ	2.7	49.3*φ	2.5	36.9	1.4	**
	EX	38	1.6	47.5*φ	1.5	47.4*φ	2.3	49.8*φ	2.5	39.7	1.9	
ICA shear	CTRL	316	11.3	314	12.1	305	14.2	304	12.9	294	16.6	
	CO2	309	15.5	372*	18.0	369*φ	17.4	362*φ	14.2	286	12.2	**
	EX	297	12.4	366*	14.6	354*φ	14.1	371*φ	18.0	298	17.0	
MCAv (cm.s^{-1})	CTRL	66	3	66	3	65	3	63	3	63	3	
	CO2	64	6	83*φ	7	83*φ	7	82*φ	7	68	5	**
	EX	58	3	75*φ	4	75*φ	5	74*φ	5	60	3	

Time: * = different from BL; p < 0.05, COND: φ = different from CTRL; ψ = different from CO_2; p < 0.01, INT: ** = significant COND x TIME interaction; φ = different from CTRL; ψ = different from CO_2; p < 0.001

Table 2. Posterior cerebral blood flow measurements during Control (CTRL), carbon dioxide (CO2), and Exercise (EX) interventions (n=8)

		Time (min)								
Measure	**Condition**	BL		15		25		Post		Int
		Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
MAP (mmHg)	CTRL	92	3	93	3	90	4	93	4	
	CO2	94	3	102	5	106*φ	6	98	5	**
	EX	87	4	102*φ	3	101*φ	3	88	4	
HR (BPM)	CTRL	63	2	65	3	65	3	64	3	
	CO2	64	2	69	3	72*φ	3	65	3	**
	EX ψ	68	2	114*φψ	2	118*φψ	2	80*φψ	3	
PetO2 (mmHg)	CTRL	97.5	2.4	104.7	5.3	100	1.4	99.3	1.3	
	CO2 φ	97.5	2.4	129.9*φ	0.8	130.3*φ	1.3	100.1	0.9	**
	EX φ ψ	95.9	1.7	94.1 φψ	3.0	96.0ψ	2.2	97.9	1.6	
PetCO2 (mmHg)	CTRL	40.2	2.3	36.7	4.5	40.2	2.2	41	0.9	
	CO2 φ	41.3	1.3	46.4*φ	0.8	46.1*φ	1	41	0.9	**
	EXφ	41.4	1.1	45.7φ	1.9	44.5	1.5	40.1	1.1	
Q_{VA} ($ml.min^{-1}$)	CTRL	113	20.6	111	21.6	103	19.7	103	17.9	
	CO2	100	13.1	141*	16.1	142*	20	95	12.9	**
	EX	90	16.1	140*	26.2	143*	26.1	87	12.3	
VA Diam (cm)	CTL	3.9	0.1	3.9	0.2	3.9	0.2	3.9	0.1	
	CO2	3.9φ	0.2	4.2φ	0.2	4.2*φ	0.2	4.0φ	0.1	**
	EX	3.7φ ψ	0.2	3.9*ψ	0.2	4.1*ψ	0.2	3.7φψ	0.1	
VA Vel ($cm.s^{-1}$)	CTRL	27.7	3.3	27.3	3.3	25.5	2.9	24.4*	3	
	CO2	24.7 φ	1.9	31.6* φ	2.2	31.2*	2.2	23.4	2	**
	EX	24.7 φ	2.0	31.1* φ	2.6	31.5*	2.5	24.1	1.7	
VA shear	CTRL	282	28	279	27	261	25	249*	26	
	CO2	251 φ	14	305*φ	19	297*φ	16	237	17	**
	EX	268	16	322*φ	20	316*φ	20	261	16	
PCAv ($cm.s^{-1}$)	CTRL	49	3	47	3	47	3	46	3	
	CO2 φ	51	4	63*φ	5	63*φ	4	52	4	**
	EX	48	4	58*φψ	5	56*φψ	4	45*ψ	3	

Time: * = different from BL; p < 0.05, COND: φ = different from CTRL; ψ = different from CO_2; p < 0.01, INT: ** = significant COND x TIME interaction; φ = different from CTRL; ψ = different from CO_2; p < 0.001

Figure 1

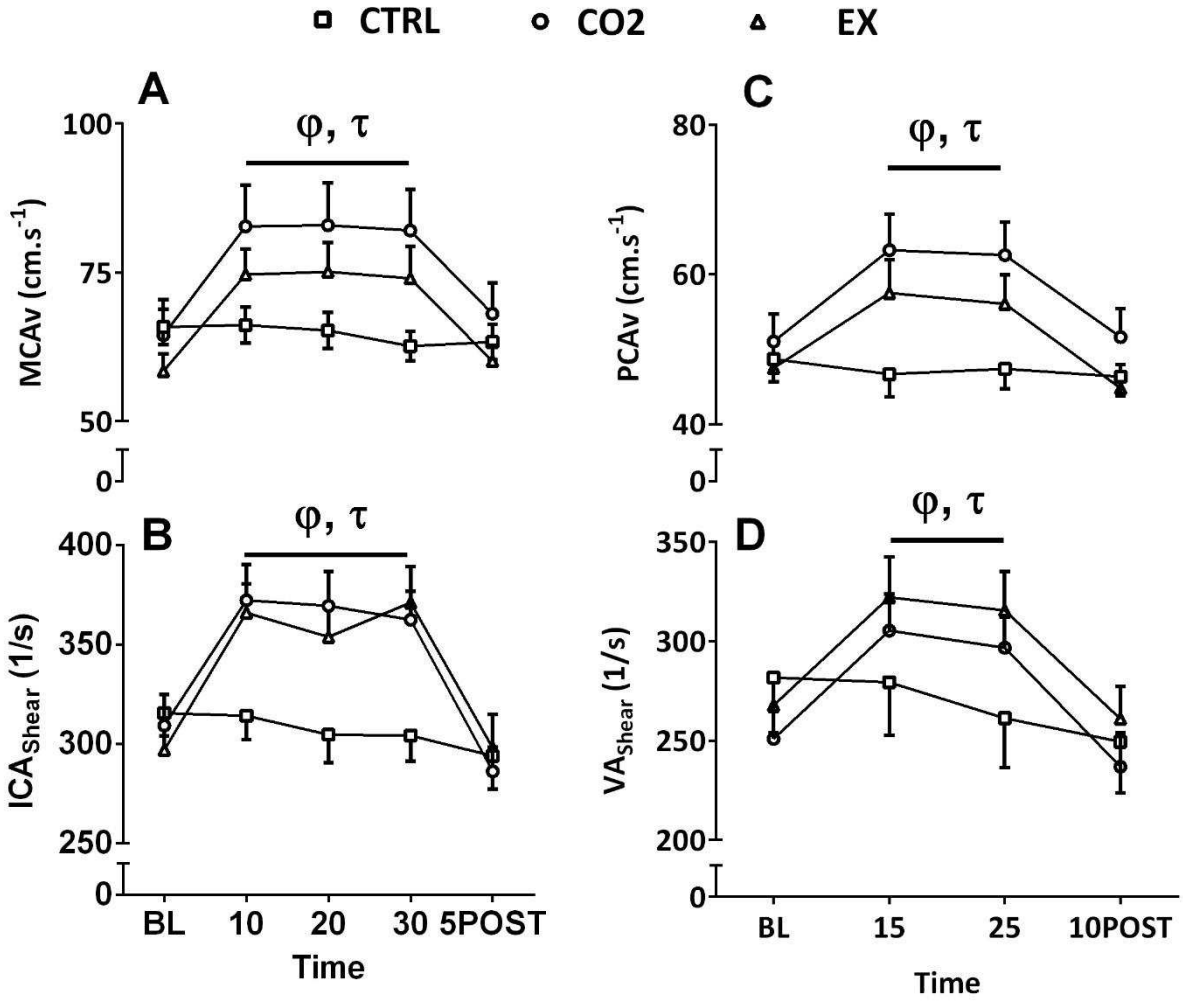
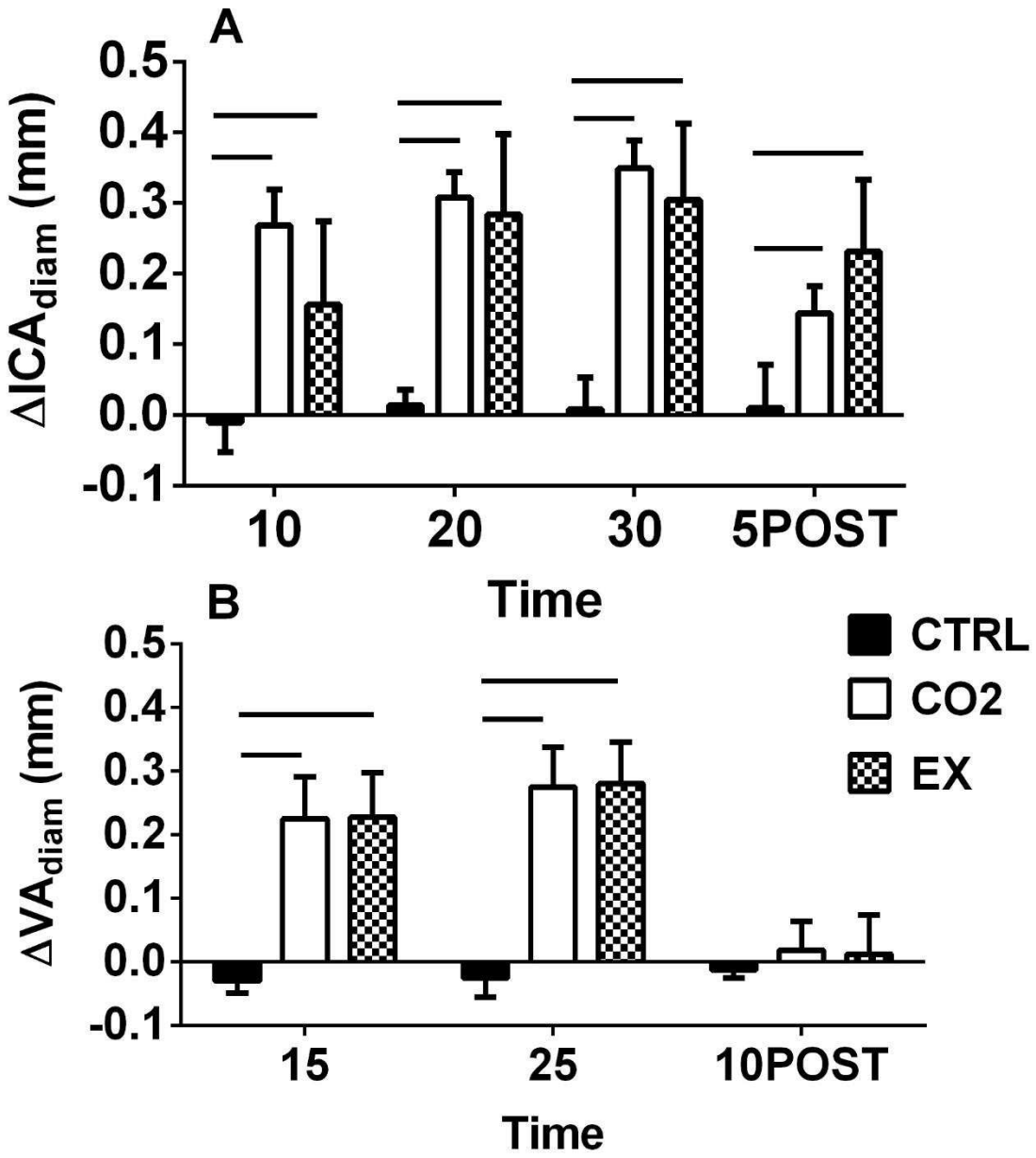

CTRL
CO2
EX
A
B
C
D
φ, τ
MCAv (cm.s-1)
PCAv (cm.s-1)
ICAShear (1/s)
VAShear (1/s)
100
75
50
0
80
60
40
400
350
300
250
200
BL
10
20
30
5POST
15
25
10POST
Time

Figure 2


A
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
ΔICA diam (mm)
10
20
30
5POST
Time
B
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
ΔVA diam (mm)
15
25
10POST
Time
CTRL
CO2
EX